

Proposed Decision Memo for Ventricular Assist Devices as Destination Therapy (CAG-00119R2)

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) proposes the following:

The evidence is adequate to conclude that VAD implantation as destination therapy improves health outcomes and is reasonable and necessary when the device has received FDA approval for a destination therapy indication and only for patients with New York Heart Association (NYHA) Class IV end-stage ventricular heart failure who are not candidates for heart transplant and who meet all of the following conditions:

a. Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,

b. Have a left ventricular ejection fraction (LVEF) < 25%; and,

c. Have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min.

CMS is not proposing changes to any other parts of Section 20.9 "Artificial Hearts and Related Devices" of the National Coverage Determinations Manual. A comparison of the current and proposed policies can be viewed in Appendix A.

We are soliciting public comments on this proposed decision pursuant to §1862(l) of the Social Security Act.

Proposed Decision Memo

To: Administrative File CAG-00119R2

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Subject: Proposed Coverage Decision Memorandum for Ventricular Assist Devices as Destination Therapy

Date: August 19, 2010

I. Proposed Decision

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a. Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,

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II. Background

Heart failure is a condition in which the heart cannot pump enough blood to the body. The incidence of heart failure rises with advancing age and continues to be a significant cause of morbidity and mortality for elderly Medicare patients. According to the Centers for Disease Control and Prevention (www.cdc.gov/dhdsplibrary/fs_heart_failure.htm), in the United States approximately 5.8 million people have heart failure with about 670,000 new cases diagnosed each year. About one in five patients with heart failure will die from the disease within one year of its diagnosis.

While heart failure is not caused by aging, the elderly are more likely to have had predisposing conditions such as long-standing hypertension (high blood pressure) or myocardial infarction (heart attack). Depending on the severity of heart failure, patients can be treated with several different types of drugs, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, digoxin, inotropes and others. Inotropes are drugs that increase the contractile force of the heart. These medications cannot reverse heart failure but may improve the symptoms of heart failure by reducing fluid, reducing strain on the heart by reducing blood pressure, slowing heart rate or making the heart beat stronger. Despite improvements in available medications and closer monitoring of patients, heart failure continues to be a progressive disease, which becomes refractory to medical management over time. Advanced or end-stage heart failure can be cured by heart transplant. Unfortunately, elderly patients are not generally candidates for transplants due to age alone or comorbid conditions, which present unacceptable surgical risks. Only about 2300 heart transplants are performed annually in the United States with available organs generally allocated to younger patients most likely to survive surgery and have a prolonged benefit (www.medhelp.org/NIHlib/GF-270.html).

The functional limitations due to heart failure can be quantified using the New York Heart Association (NYHA) classification system, which was most recently updated by the American Heart Association (AHA). In 1994, the Criteria Committee of the New York City affiliate of AHA revised the classification to describe the following functional classes of heart failure

(<http://www.americanheart.org/presenter.jhtml?identifier=4569>):

Class I

Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.

Class II

Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.

Class III

Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.

Class IV

Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

It has been noted in the literature that the NYHA classification system is often subjective with physicians having difficulty assigning patients to any one class. Therefore, in an article published in the American Family Physician (Chavey et al, 2001), the authors offer a classification scheme that they believe will result in less ambiguous patient assignment to a class. The authors present new symptomatic definitions and link them to a corresponding NYHA class or classes. In this scheme, patients with a recent history of dyspnea at rest and patients with dyspnea at rest are assigned to different classes as the authors believe this to be indicative of prognosis.

Asymptomatic – NYHA Class I

Symptomatic – NYHA Class II/III

Symptomatic with recent history of dyspnea at rest – NYHA Class IIIB

Symptomatic with dyspnea at rest – NYHA Class IV

This proposal did not become a standard for clinical heart failure classification.

Ventricular assist devices (VADs) are mechanical pumps used to assist a damaged or weakened heart in pumping blood. These devices support a patient's weakened native heart but do not replace it, unlike heart transplant. VADs are surgically attached to a ventricle of the native heart and the mechanical pump is implanted in the abdomen or in the chest cavity. The device requires a driveline that goes from the pump inside the patient's body to an external power and control unit. Typically these external portions of the device are portable and the patient can carry them in a small bag along with extra batteries. The device also has a base unit that is not portable but can be used when the patient is at home or in the hospital.

Selection criteria for severe heart failure patients who may be considered for VAD implantation include clinical assessment (NYHA functional class, clinical history, management and duration of disease, cardiopulmonary stress testing) and cardiac and anatomic considerations (body size considerations), as well as non-cardiac considerations and assessment of operative risk.

Mechanical circulatory support devices, including VADs, have been used to assist acutely injured hearts to recover from such things as infection or the effects of open heart surgery for a number of years. More recently, VADs have been used to support failing hearts over longer periods of time as a "bridge to transplant" until a suitable donor heart becomes available. Information from the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) states that at any one time 3500 to 4000 patients are listed for heart transplant but more than 25% of these patients may die before a donor heart is found (www.medhelp.org/NIHlib/GF-270.html). With the advent of improvements in the reliability and durability of VADs some patients on transplant waiting lists actually recovered cardiac function and were able to have their devices removed. Still other patients received newer smaller devices, which enabled them to leave the hospital and return home, sometimes for long periods, while awaiting transplant. Even patients with end-stage heart failure who are not transplant candidates have achieved improved survival with permanent VAD support through destination therapy (DT). As the number of patients attaining long-term survival with VADs continues to rise, new research seeks to expand the indications for VAD implantation to include patients in earlier stage heart failure to prevent development of unsurvivable comorbidities which could limit the clinical benefit of a VAD.

In November, 2002, based on the successful completion of the REMATCH clinical trial the FDA expanded the approved indications for a previously approved bridge device (HeartMate™ SNAP VE LVAS) for use by end-stage, non-transplantable patients as permanent or "destination therapy." That approval stated: "This device is now also indicated for use in patients with New York Heart Association Class IV end-stage left ventricular failure who have received optimal medical therapy for at least 60 of the last 90 days, who have a life expectancy of less than two years, and who are not eligible for cardiac transplantation."

On January 20, 2010, a second device (HeartMate II™) was approved by the FDA as destination therapy "for use in patients with New York Heart Association (NYHA) Class III B or IV end-stage left ventricular failure, who have received optimal medical therapy for at least 45 of the last 60 days and are not candidates for cardiac transplantation." The HeartMate II is a continuous-flow device weighing approximately one pound. It is "implanted below the heart with its entrance attached to the left ventricle and its exit connected to the aorta...Blood flows from the heart into the pump. A small electric motor in the pump drives a rotor inside the pump which pushes blood into the aorta and out to the body. A flexible tube passes through the patient's skin and connects the implanted pump to a small controller worn outside the body. The controller is powered either by batteries or connected by means of a power supply to a standard household electrical power outlet."

(<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm201473.htm>) The patient population on which the new device was studied was more diverse than that in the REMATCH trial, and had somewhat different patient selection criteria than the earlier destination patients.

III. History of Medicare Coverage

On October 1, 2003, Medicare began covering VAD implantation as destination therapy for beneficiaries with certain clinical indications. This decision was based primarily on the results of the REMATCH study which randomized end stage heart failure patients to receive either the HeartMate SNAP VE device or medical management.

In addition to limiting coverage to specified clinical indications, Medicare required that devices be used according to their FDA label and instituted requirements for hospitals in which the procedure takes place (e.g., surgeon experience, registry participation, hospital infrastructure, clinical expertise and patient support). These were efforts to ensure that the outcomes achieved in the REMATCH study would be replicated outside the study.

In 2007, with the patient clinical indications remaining unchanged, CMS updated the hospital criteria to require hospitals to be certified by the Joint Commission under the Disease Specific Certification Program, adjusted the minimum experience of the surgeon and identified the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) as the required registry.

Section 20.9 of the National Coverage Determinations Manual titled "Artificial Hearts and Related Devices" is reprinted in its entirety in Appendix B.

Current Request

CMS received a request from Thoratec, Inc. to reconsider Section 20.9 of the National Coverage Determinations Manual related to VADs used as destination therapy, based on the outcomes of the HeartMate II Destination Therapy study. Specifically, Thoratec requested expanding coverage to include patients with NYHA Class IIIB symptoms, to reduce the required time on optimal medical management to 45 of the last 60 days, to include time on a balloon pump or inotrope therapy as indications for coverage, to increase the peak oxygen consumption to < 14 ml/kg/min and to remove the body size requirement. The request did not include changes to other portions of the NCD (facility criteria, post-cardiotomy or bridge to transplant indications).

CMS is focusing this review on the patient selection aspect of the policy and is not reviewing other portions of the NCD as part this analysis.

Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category under Part A or Part B as a prerequisite to Medicare coverage. VADs may fall within the Inpatient Hospital Services benefit category (section 1861(b)(2) of the Social Security Act (the Act)), which describes supplies, appliances, and equipment furnished by the hospital, for use in the hospital, for the care and treatment of inpatients. After a VAD has been surgically implanted into the patient and when the patient is not a hospital patient, the replacement of an external part or parts may be covered under Medicare Part B within the Prosthetic Device benefit category (section 1861(s)(8) of the Act). This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

February 22, 2010 CMS opens a National Coverage Analysis to reconsider the patient population covered for the implantation of a VAD as destination therapy.

March 24, 2010 The initial 30-day public comment period closes.

V. FDA Status

HeartMate II LVAS

On January 20, 2010, Thoratec Inc. received FDA approval to expand the labeled indication for the HeartMate II Left Ventricular Assist System to include patients that are not candidates for heart transplantation. The device was approved in 2008 for a bridge to transplant indication. As stated in the FDA approval letter (http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040S005a.pdf), the device indication is as follows:

This device is indicated for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. It is now also indicated for use in patients with New York Heart Association (NYHA) Class IIIB or IV end-stage left ventricular failure who have received optimal medical therapy for at least 45 of the last 60 days, and are not candidates for cardiac transplantation. The HeartMate II LVAS is intended for use both inside and outside the hospital, or for transportation of ventricular assist device patients via ground ambulance, fixed-wing aircraft, or helicopter.

HeartMate II is a continuous-flow (non-pulsatile) ventricular assist device that is smaller in size than previously FDA approved devices.

HeartMate XVE LVAS

On April 4, 2003, Thoratec Inc. received FDA approval to expand the labeled indication for the HeartMate XVE to include patients that are not candidates for heart transplant. The device was previously approved for a bridge to transplant indication. As stated in the FDA approval order statement

(<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pmasimplesearch.cfm?db=pma&id=13984#aostatement>), the device indication is as follows:

Approval for an expanded indication for use for the thoratec heartmate xve lvas. This device system is indicated for use as a bridge to cardiac transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. It is now also indicated for use in patients with new york heart association class iv end stage left ventricular failure who have received optimal medical therapy for at least 60 of the last 90 days, and who have a life expectancy of less than two years, and who are not eligible for cardiac transplantation. The device system is approved for use both inside and outside the hospital.

The HeartMate XVE is a pulsatile device that requires a minimum body surface area of 1.5m² for implantation.

VI. General Methodological Principles

When making national coverage decisions under section 1862(a)(1)(A) of the Social Security Act, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix C. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will not be made available to the public. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

Our review focuses on published evidence related to four patient selection criteria from the HeartMate II destination therapy study that Thoratec is requesting be reflected in Medicare coverage. Currently, the HeartMate II study entry criteria and the current destination therapy NCD differ in these areas: 1) heart failure classification, 2) time on optimal medical management, inotropes and balloon pump, 3) peak oxygen consumption, and 4) body surface area (BSA).

In this coverage analysis, we considered destination therapy studies and evidence that were published since the last reconsideration in 2007. It incorporates all evidence from prior decision memoranda regarding this issue. A summary of the body of evidence reviewed to date in developing this decision memorandum is available via the final decision memoranda released following the completion of each of the prior national coverage analyses (NCAs) for reconsiderations of the artificial heart and related devices NCD (<http://www.cms.gov/mcd/viewdecisionmemo.asp?id=79> and <http://www.cms.gov/mcd/viewdecisionmemo.asp?id=187>).

The significant outcomes of interest related to VAD implantation are all-cause mortality, quality of life and adverse events. As discussed in the decision memorandum from 2003 when the REMATCH study was evaluated, an advantage in mortality as the result of this or any other therapy, however, must be weighed against the likelihood of adverse events or other negative consequences associated with its use, such as infection, prolonged hospitalization, or increased bleeding. In addition to these outcomes of interest, we are focusing on information related to patient selection criteria so patients can be appropriately and carefully selected for the procedure.

Literature Search

A PubMed search was performed with the search terms [destination therapy] AND [[ventricular assist device] or [HeartMate II]]. After reviewing abstracts, CMS limited the review to studies that involved the HeartMate II device and/or addressed one of our evidence questions (outlined below in B.1.). Two studies related to the HeartMate II destination therapy pivotal trial were selected for review (Slaughter, et al. 2009 and Rogers, et al. 2010). Focused searches were conducted on evidence question topics (VAD patient selection criteria, heart failure classification, peak oxygen consumption and body size) and the reference lists of full text articles were reviewed for relevant articles. Articles by Lang et al. 2007, Musci et al. 2008, and Lietz et al. 2009 were identified.

In addition, CMS located the published FDA Summary of Safety and Effectiveness and includes that document in the body of evidence. The Summary of Safety and Effectiveness was located by searching the FDA website (www.fda.gov) using the search terms [HeartMateII] AND [destination therapy].

Searches of PubMed using the search terms [NYHA classification iiib, IIIB, iiib/iv and IIIB/IV] did not result in locating an accepted standard definition of NYHA Class IIIB heart failure.

B. Discussion of evidence reviewed

1. Question

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:

- a. *are said to have NYHA Class IIIB symptoms?*
- b. *have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or patient is balloon pump dependent for 7 days, or IV inotrope dependent for 14 days?*
- c. *have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min if not contra-indicated?*
- d. *have a body surface area of $<1.5m^2$?*

2. External Technology Assessment

CMS did not locate nor commission an external technology assessment for this decision.

3. Internal Technology Assessment

Slaughter MS et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361:2241-51.

Methods: This pivotal trial had two arms with 134 patients randomized to receive the continuous flow HeartMate II and a 66 patient active control arm, whose patients were to receive the pulsatile HeartMate XVE. According to the publication, "Enrolled patients met the following criteria: a left ventricular ejection fraction [LVEF] of less than 25%; a peak oxygen consumption of less than 14 ml per kilogram of body weight per minute, or less than 50% of the predicted value; and New York Heart Association (NYHA) class IIIB or IV symptoms for at least 45 of the 60 days before enrollment or dependence on an intra-aortic balloon pump for a period of 7 days or inotropes for a period of at least 14 days before enrollment." Subsequent to randomization eight patients were not implanted with a device and four patients were implanted with a device outside their randomization assignment. Therefore 133 patients received a HeartMate II and 59 patients initially received the HeartMate XVE and their data were reported in an intention to treat and as-treated basis.

The primary composite endpoint of the study was 2 years post-implant survival, free of stroke resulting in a Modified Rankin Score > 3 or reoperation to repair or replace the device. The Modified Rankin Score is a functional assessment that ranges from zero (no symptoms at all) to six (dead). There were no stated goals for the number patients in either NYHA Class IIIB or Class IV in either arm. Definitions of Class IIIB or Class IV heart failure were not included in the published study or published supplemental material.

Thoratec provided CMS with the following unpublished definitions of Class IIIB and Class IV heart failure as utilized in the pivotal study protocol:

NYHA Class IIIB:
Cardiac disease resulting in marked limitations of physical activity. Patients are comfortable at rest. Mild physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

NYHA Class IV:
Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Results: The patients in both arms had similar baseline characteristics (Table 1):

Table 1: Baseline characteristics of the study patients, according to treatment group (Slaughter et al., 2009).		
Characteristic	HeartMate II	HeartMate XVE
Age—yr.		
Mean	62 ± 12	63 ± 12
Median (range)	64 (26-79)	65 (29-81)
Male sex—no. (%)	108 (81)	61 (92)
LVEF	17.0 ± 5.5	16.8 ± 5.4
Ischemic heart failure—no. (%)	88 (66)	45 (68)
Intravenous inotrope—no.(%)	103 (77)	55 (83)
Biventricular pacemaker	85 (63)	39 (59)
ICD	111 (83)	52 (79)
Intra-aortic balloon pump	30 (22)	15 (23)

Among the 181 patients assessed for NYHA class at baseline, 5 were class IIIA (undefined in the study), 38 were class IIIB, and 138 were class IV. Neither the published study nor the published supplement accompanying it gave any breakdown by NYHA class of the patient characteristics or outcomes.

The primary endpoint (2-year post implant survival free of stroke) of the pivotal study reported on an intent to treat basis was met by 62 of the 134 patients (46%) in the continuous-flow device arm and 7 of the 66 patients (11%) the pulsatile device arm. The first occurring reason for failing to achieve the composite endpoint in the HeartMate II trial differed by device (Table 2).

Table 2. Primary endpoint according to treatment group (Slaughter, et al. 2009):

	HeartMate II	HeartMate XVE	P Value
Stroke (Rankin score > 3)	15 (11%)	8 (12%)	0.56
Reoperation (pump/repair replace)	13 (10%)	24 (24%)	< 0.001
Death within 2 yrs of implantation	44 (33%)	27 (41%)	0.048
Any (primary endpoint)	72 (54%)	59 (89%)	< 0.001

Table 3. Functional status and quality of life, reported on an as-treated basis, according to time since device implant (Slaughter et al., 2009).

	Baseline	HeartMate II 3Mo	12Mo	24Mo
NYHA class				
No. of patients tested (no./%)	126	91	72	50
Class I	0	30 (33)	30 (42)	21 (42)
Class II	0	38(42)	25 (35)	19 (38)
Class IIIB	27 (21)	5 (5)	4 (6)	1 (2)
Class IV	95 (75)	2 (2)	0	3 (6)
No. patients tested (no./%)				
Six Minute walk	50	77	61	36
Distance <i>m</i>	182 ± 140	319 ± 191	318 ± 164	377 ± 191
Minnesota Living with Heart failure questionnaire				
Score	116 75.4 ± 17.7	89 37.4 ± 22.2	76 34.1 ± 22.4	44 29.6 ± 22.4
Kansas City Cardiomyopathy questionnaire				
Overall summary score	115 27.4±16.3	89 63.4 ± 18.5	76 65.9 ± 20.0	47 69.9 ± 18.7
Clinical summary score		35.1±18.5	47.2 ± 17.4	68.6 ± 21.8 72.9 ± 19.3

Data on functional status and quality of life for patients who received the pulsatile device demonstrate improvements over time (Table 3). We have not reproduced the data for the pulsatile device as it is not the subject of this decision. The entire table is included in the published article.

Adverse events and associated relative risks were reported on an as treated basis with results for the continuous-flow device patients showing lower risk in all measures (not all were statistically significant). Lowered risk reached statistical significance for pump replacement, sepsis, medical management (with inotropes) of right heart failure, respiratory failure and renal failure. While continuous-flow patients demonstrated lower risk, their absolute adverse event rates are important to note. Of the continuous-flow patients, 35% experienced a VAD related infection, 36% had sepsis, 16% had renal failure and 30% had bleeding requiring surgery and 18% had a stroke.

Authors' Conclusions: The investigators concluded that the "study shows improvements in the rate of survival, quality of life, functional capacity of patients, and device durability with the continuous-flow...device as compared to the pulsatile-flow...device" and support its use "to provide long-term hemodynamic support that is linked to improvements in longevity and quality of life."

FDA Summary of Safety and Effectiveness. PMA number P060040/S005. January 10, 2010.

This document describes the evidence considered by FDA in evaluating the HeartMate II for destination therapy. A central consideration is the pivotal trial which compared the HeartMate XVE to the HeartMate II for use in destination therapy, reported by Slaughter et al. but with independent FDA data analysis. Effectiveness of the HM II was evaluated using a composite endpoint including survival at 2 years, free of stroke resulting in a Modified Rankin Score > 3 or reoperation to repair or replace the device. Safety was documented by incidence of adverse events and device malfunctions and failures compared to the XVE. Secondary objectives evaluated included separate evaluations of each component of the endpoint, functional status (6-minute walk, patient activity score, and NYHA class), health status including quality of life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy Questionnaire), all adverse events, re-operations, re-hospitalizations, and neurocognitive assessments (memory, language, visual/spatial perception, processing speed and abstract/executive function).

Methods: The study design was a prospective, randomized, unblinded, non-inferiority evaluation of HM II in end-stage left ventricular failure patients who were not candidates for heart transplant and were refractory to optimal medical therapy. The protocol's analysis plan specified testing for superiority once non-inferiority was established. Two patients were randomized to HM II for every patient randomized to XVE. Randomization was stratified by study center and blocked to maintain the 2:1 ratio over time. Two hundred patients were enrolled into the Primary Cohort (134 HM II and 66 XVE) at 38 sites from March 2005 to May 2007. All 200 patients in the Primary Cohort were followed for at least two years.

Four additional cohorts were considered by FDA in their evaluation:

- Small BSA Cohort: 24 patients with BSA < 1.5m² who could not be randomized to XVE due to its size.
- XVE Exchange Cohort: 123 failed XVE patients who received HM II as a replacement.
- Randomized Continued Access Protocol (CAP) Cohort: 187 patients enrolled under the primary cohort protocol after the primary cohort had been filled.
- Anatomic Deviation Cohort: 99 patients with BSA > 1.5m² who could not be randomized to XVE due to body habitus or other anatomic considerations.

Patients meeting the study endpoint were considered a success and a failure if not. Patients urgently transplanted due to device failure were study failures. Patients electively transplanted after reversal of a pre-enrollment co-morbidity were followed and considered a success if they ultimately achieved the composite endpoint within 2 years of VAD implant.

Results: Reasons for patient ineligibility for transplant included age (28%), recent cancer history (9%), obesity (7%), and substance abuse or insufficient social support (7%). Patient age range 26 to 81 yrs, median 64 yrs. No significant differences in age, BSA, body mass index (BMI), etiology or ethnicity between HM II and XVE groups. HM II group contained 19% females and XVE 8%, but, overall, males with ischemic disease predominated. Notable in patient history: 83% of patients entered the study with ICDs and 16% had a history of stroke; 79% of patients on inotropes at baseline; 23% on intra-aortic balloon pump; and 8% on mechanical ventilation (indications of end-stage heart failure).

Table 4: As treated analysis of patient survival at 2 years by original implanted device. 62/134 HM II (46%) and 7/66 XVE (11%) patients achieved the composite endpoint:

	HM II (n 133)	XVE (n 59)
Ongoing on original device	50(38%)	0 (0%)
Ongoing with replacement same type device	12 (9%)	2 (3%)
Ongoing with replacement alternate type device	0 (0%)	14 (24%)
Transplanted	13 (10%)	8 (19%)
Explanted for recovery	1 (1%)	1 (1%)
Total	76 (57%)	25 (42%)

The primary causes of death of the 57 HM II patients were: Stroke—13 pts (10%); right heart failure—8 pts (6%); device malfunction (loss of power, device thrombosis, VAD dysfunction)—10 pts (8%). In 34 XVE patients causes of death were: Stroke—11 pts (19%); right heart failure—5 pts (8%); infection—6 pts (10%); multi-system organ failure—4 pts (7%).

There is no discussion of nor data relating to NYHA class IIIB in this document. The only mention of NYHA class is found in a bar graph used to show surviving patients functioning at Class I or II functional level after implantation over the course of the study. According to the graph 98% of 58 evaluable HM II patients and 100% of 2 evaluable XVE patients achieved this level at 24 months.

FDA Conclusions: "The composite endpoint analysis showed the HeartMate II to be superior to the control HeartMate XVE device. In addition, both intent to treat and per protocol analyses demonstrated a Kaplan Meier survival advantage with the HeartMate II compared to control. No safety or engineering problems were detected that suggested that the increased benefit seen with the HeartMate II device was accompanied by significantly increased risk compared to the HeartMate XVE control. Hence, a favorable risk-benefit profile has been established for the HeartMate II device."

Data from the 24 patient Small Body Cohort are not included in the document, which concludes, "Because of its small size, the HeartMate II LVAS can be used in the treatment of smaller sized non-cardiac transplant patients. These smaller sized patients include mostly women and men of small stature. It can also be used in patients with anatomic features that preclude use of the larger HeartMate XVE device."

Rogers JG et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol. 2010;55:1826-34.

Methods: This article discusses data on use of the HeartMate II in both bridge to transplant (BTT) and destination (DT) patients between 2005 and 2009 in studies sponsored by Thoratec at 38 U. S. centers. A total of 374 destination patients in NYHA functional classes IIIb and IV heart failure, ineligible for transplant and refractory to optimal medical management are included in the report. This includes the trial data reported by Slaughter et al. and analyzed by FDA, as well as the additional cohorts analyzed by the FDA. There is no definition of NYHA class IIIb heart failure included in the paper and the results do not subdivide class III.

Results: Detailed baseline data for DT patients included mean age 63 ± 12 , 27% female, 58% ischemic etiology of heart failure, LVEF $17.1\% \pm 5.8$, 72% cardiac resynchronization therapy (CRT), 77% history of intravenous inotropes, 21% had been treated with intra-aortic balloon pump. There is no breakdown by functional class included in the baseline data, other than the comment that "most patients had NYHA functional class IV symptoms at baseline." At one month following implantation 47% of destination therapy patients are reported as improved to class I or II. "Approximately 80% of destination therapy patients remained in NYHA functional class I or II from 6 through 24 months."

Additional information about on-going destination therapy testing with HeartMate II is included in this article in bar graph format showing that of 353 patients receiving the device for destination therapy approximately 30% were in NYHA class III, but subclassification A or B was not specified. In summary the article reports that 80% of 245 destination therapy patients at 6 months and 79% of 99 destination therapy patients at 24 months had improved to NYHA class I or II. No information about overall survival or complications is reported in this article.

Authors' conclusions: "HeartMate II LVAD support in both the bridge to transplant and destination therapy applications result in early, sustained, and clinically meaningful improvements in functional capacity and heart failure-related quality of life."

Lang CC, Agostoni P, Mancini DM. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. J of Cardiac Fail. 2007;12(8):672-9.

This review article discusses the need for reliable prognostic indicators for evaluation of candidates for heart transplant in view of the widening gap between number of surgical candidates and available organs. The authors note that the American Heart Association has recommended use of peak VO_2 , specifically ≤ 14 ml/min/kg, as a criterion for acceptance of ambulatory patients for transplant.

Measurement of peak VO_2 in congestive heart failure patients can, however, be confounded by comorbidities and non-cardiac factors such that some other authors have questioned its usefulness. Various studies and methods tested for alternate measurements of hemodynamic dynamic response to exercise are briefly reviewed. The authors point out that VO_2 is an indirect measure of cardiac output (CO), which cannot be easily measured directly, and provides an index of cardiac reserve in CHF patients.

They conclude noninvasive methods of measuring cardiac output will require larger clinical trials to determine their prognostic value. In the mean time "the clinical usefulness of peak VO_2 was established by a large body of data acquired over two decades and is now widely used."

Lietz K, Miller LW. Patient selection for left ventricular assist devices. Curr Opin Cardiol. 2009;24:246-251.

This review article reviews indications for implantation of LVADs for both bridge to transplant and destination therapy and discusses in detail patient considerations that impact selection of appropriate candidates. Patients must be fully and carefully assessed to determine the severity of their heart failure and what benefits they are likely to derive from device use. Cardiogenic shock and worsening symptoms in inotrope-dependent patients are identified as accounting for 60% of implantations. Timing of device placement is important as heart failure is progressive and patients can become too severely compromised to derive survival benefit from it. In less ill patients, risk scoring may be helpful in determining the likely impact of a device on survival.

Specific considerations which should be evaluated in addition to cardiac function include right ventricular function, arrhythmias, anatomy and body habitus. Noncardiac considerations include patient age, comorbidities, psychiatric and social issues. Risk scoring guides can be used to assess the possibility of in-hospital mortality. The authors conclude: "Appropriate assessment of candidates for LVAD implantation is of paramount importance. As technology will continue to advance and new devices provide life-saving treatment, more research will be needed to better understand the key determinants of successful operative and long-term VAD outcomes."

Musci M, Loforte A, Potapov EV, et al. Body mass index and outcome after ventricular assist device placement. Ann Thorac Surg. 2008 Oct;86(4):1236-42.

Methods: A retrospective analysis of 590 consecutive patients with advanced heart failure who underwent VAD placement between 1996 and 2006 at Berlin. Patients were divided into five groups based on body-mass index (BMI, kg/m²) (< 20; 20-24; 25-29; 30-35; and > 35). Twenty patients comprised the group with BMI < 20. In a multivariate analysis adjusted for age, sex, diagnosis, emergency level, and type of device (left ventricular or biventricular assist device), procedural success (recovery, transplantation, or 30-day survival) and complications were analyzed. The best group was set as reference category for calculation of odds ratios.

Results: The groups with both extremes of BMI had the worst outcomes. The best procedural success was in the group with BMI 25 to 29 kg/m². Underweight patients had similar survival rates to patients with normal weight. The unadjusted odds ratio of 30-day mortality for BMI < 20 kg/m² was 2.1 (95% confidence interval 0.9-4.7, p = .05) compared with the 25-29 BMI group. Overweight and obese patients did not have decreased survival. Extreme obesity at the time of VAD implantation showed elevated risk for postoperative death. There was no significant difference for BMI groups in the type of complications and cause of death. Cumulative survival curves for BMI category and overall VAD patient survival showed no significant differences. There were no significant differences in cause of death by BMI group.

Authors' Conclusions: "Cardiac cachexia [muscle wasting and general debility that can occur during a chronic disease] need not be an exclusion criterion for VAD placement. Underweight patients appear to have benefit from mechanical support. Severely obese patients should be carefully selected before VAD placement."

4. MEDCAC

A meeting of the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) was not convened for this analysis.

5. Evidence-based guidelines

Evidence-based guidelines regarding the use of mechanically assisted circulatory support were not located. CMS also searched for guidelines regarding the treatment of heart failure and heart failure classification systems; one guideline and one guideline update was located.

Hunt SA et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at: <http://www.acc.org/clinical/guidelines/failure//index.pdf>.

Hunt SA et al. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. Circulation. 2009;119:e391-e479.

The American College of Cardiology (ACC) and the American Heart Association (AHA) first published guidelines for the evaluation and management of heart failure (HF) in 1995. Those guidelines were updated in 2001 and 2005 and a focused update was published in 2009. The 2001 document introduced a new classification system for describing the development and progression of heart failure. In this four stage system the first two stages (A and B) are designed to provide early identification of patients at risk for developing heart failure. Stage C describes patients with current or past symptoms of heart failure and underlying structural disease (majority of patients). Stage D describes patients with refractory heart failure requiring specialized treatments which may include mechanical circulatory support. This new "classification system is intended to complement but in no way replace the New York Heart Association functional classification, which primarily gauges the severity of symptoms in patients who are in Stage C or D...although symptoms (NYHA class) might vary widely over time (in response to therapy or to progression of disease) in a patient who has already developed the clinical syndrome of HF (Stage C), the patient could never return to stage B (never had HF) ..."

There are no definitions of the NYHA functional classifications included the ACC/AHA Guidelines. The authors note that this classification system "reflects a subjective assessment by a healthcare provider and can change frequently over short periods of time." "A variety of approaches have been used to quantify the degree of functional limitation imposed by HF. The most widely used scale is the NYHA functional classification, but this system is subject to considerable interobserver variability and is insensitive to important changes in exercise capacity... Maximal exercise testing, with measurement of peak oxygen uptake, has been used to identify appropriate candidates for cardiac transplantation, to determine disability, and to assist in the formulation of an exercise prescription, but its role in the general management of patients with HF has not been defined."

In the section on detailed recommendations for patients with refractory End-Stage Heart Failure (Stage D) both the 2005 guidelines and the 2009 focused update state "Consideration of an LV assist device as permanent or 'destination' therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy." This was rated class IIa, level of evidence: B, and is based upon the REMATCH trial results. The authors comment that, "Presently, destination device therapy is anticipated to benefit those patients predicted to have a 1-year survival of less than 50%. One such group could be the population of non-transplant-eligible patients requiring continuous intravenous inotropic infusions."

The authors list as a relative indication for heart transplant, "Peak VO_2 11 to 14 mL per kg per minute (or 55% predicted) and major limitation of the patient's daily activities."

6. Professional Society Position Statements

If we receive professional society position statements on this proposed decision we will review them as we develop our final decision.

7. Expert Opinion

Expert opinion was not solicited beyond the public comment process.

8. Public Comments

Initial 30-day comment period

Seven comments were received during the initial comment period, all addressing the NYHA Class IIIB heart failure population. Two commenters favored the inclusion of Class IIIB patients in national coverage while five commenters stated coverage for Class IIIB should be limited to clinical studies.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1862(l) of the Act.) In order to be covered by Medicare, an item or service must first fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A) of the Act. This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment.

We address each of the analytic questions below.

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:

- a. *are said to have NYHA Class IIIB symptoms?*

The NYHA classification system was developed in 1928 as a method of describing both the severity and prognosis for heart failure patients. It can also be used to assess response to treatment (Table 3). When last revised in 1994, none of the four classes contained a subclassification. Class III is defined as: "Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or angina pain." Class IV is defined as: "Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased." While its use is long-standing and widespread, the NYHA class is not very reproducible and doesn't reliably predict the walking distance or exercise tolerance on formal testing. Class III includes a number of subjective elements, e.g., "marked limitation," and "less than ordinary activity." The definition of Class IIIB in Chavey et al. (2001), "recent history of dyspnea at rest," differs from the unpublished definition provided by Thoratec. The subclassification IIIB is not widely accepted, does not appear in professional society guidelines or position statements, and appears in few citations in the published peer-reviewed medical literature outside of the Slaughter et al. 2009 and Rogers et al. 2010 articles.

Since 1980 the American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly produced guidelines for the treatment and diagnosis of heart failure. The 2001 update of these guidelines included a new approach to classification of heart failure that emphasized both the development and progression of the disease with definition of four stages. The 2009 update to the guidelines states: "Stage D designates patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as mechanical circulatory support, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation..." Stage C "denotes patients with current or past symptoms of HF associated with underlying structural heart disease (the bulk of patients with HF)." Stage D appears most closely related to NYHA Class IV, but Stage C does not appear to describe patients with such advanced disease.

No definition of NYHA Class IIIB was found by CMS in reviewing both the published trial results (Slaughter, et al. 2009) and the FDA's Summary of Safety and Effectiveness

(http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040S005b.pdf). The study enrolled 31 Class III patients (4 Class IIIA and 27 Class IIIB) in the HeartMate II arm of the study and 12 Class III patients (1 Class IIIA and 11 Class IIIB) in the HeartMate XVE arm. However, neither the published report of the pivotal HeartMate II destination therapy trial nor the supplementary material accompanying it provided information about differences in outcomes between patients in NYHA class III vs. class IV.

We are aware that additional destination therapy patients outside of the pivotal group have been implanted, both as part of a continued access protocol and in several cohort studies; however detailed data by NYHA class for these patients including outcomes and complications have not been published.

While the pivotal study (Slaughter, et al. 2009) achieved overall good outcomes, Class III patients represent only about one-fourth of the enrolled patients. We have significant concern regarding the ability to replicate the study outcomes in the IIIB population outside of the controlled study. We do not believe the classification IIIB is generally accepted. Class IIIB is not a heart failure class that is included in the current ACC/AHA guidelines regarding heart failure and we are not aware that it is a classification commonly in use by heart failure specialists. Therefore, we do not believe it would be possible to identify patients accurately enough to replicate the study's selection criteria in routine clinical practice.

We propose that the evidence is not adequate to conclude that patients who have been classified by some as having Class IIIB heart failure have improved outcomes after VAD implantation. Therefore we propose to continue coverage only for Class IV heart failure patients. The current NCD as written, which we do not propose changing, allows coverage of other patient populations and indications within Investigational Device Exemption (IDE) trials and as routine costs in clinical trials defined under section 310.1 of the NCD manual. To make a consistent policy, we also propose to delete the following phrase, "and the device is used according to the FDA approved labeling instructions."

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:

- b. *have failed to respond to optimal medical management (including beta-blockers and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or patient is balloon pump dependent for 7 days or IV inotrope dependent for 14 days?*

VAD implantation is typically not considered until heart failure has progressed to the point that medical management is failing to control symptoms. The current NCD requires optimal medical management for 60 of the last 90 days (67%), while the HeartMate II study (Slaughter, et al. 2009) required optimal medical management for 45 of the last 60 days (75%) for enrollment and demonstrated improved health outcomes. While over a shorter period of time, we believe this is a more intensive medical requirement when percent time is considered. Balloon pump and inpatient inotrope therapy indicate that a patient has been unresponsive to conventional medical management and required prolonged hospitalization, possibly with intensive care, for a heart failure episode. The current NCD does recognize that "continued need for intravenous inotropic therapy" may be an indication for VAD implantation, and we are proposing to combine it with the other indications based upon medication management and specify a minimum length of treatment to qualify.

We believe that the evidence is adequate to conclude that patients that have failed to respond to optimal medical management for 45 of the last 60 days, or are balloon pump dependent for 7 days or IV inotrope dependent for 14 days have improved health outcomes after VAD implantation and propose that this should be included in the coverage criteria.

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:

- c. *have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min if not contra-indicated?*

The peak oxygen consumption (VO_2max) is based upon a cardiopulmonary stress test. This test shows the maximum amount of oxygen the heart can provide to the muscles during sustained activity. VO_2max is the point at which the body cannot increase its intake of oxygen despite an increase in exercise intensity. This measure is a predictor of poor prognosis at very low levels. Commonly, a $\text{VO}_2\text{max} \leq 14$ (in ml/kg/minute) is used as a criterion for heart transplant eligibility.

During the REMATCH trial, which supported the original approval for destination therapy, after 18 months of enrollment, the entry criteria were slightly modified in an effort to recruit more patients. Qualifying peak O_2 consumption was modified to ≤ 14 ml/kg/min. We noted at the time that 3 LVAD patients were enrolled under the modified criteria, but because of that small number we opted to specify the O_2 consumption level of 12 ml/kg/min that was the original requirement for trial entry as the inclusion requirement in the final coverage decision.

In a 2007 review article by Lang et al looking at the prognostic significance of exercise induced hemodynamic variables in heart failure the authors noted that "clinical usefulness of peak VO_2 was established by a large body of data acquired over two decades and is now widely used." The American College of Cardiology/American Heart Association guidelines recommend that peak VO_2 can help determine timing for heart transplant, noting "that transplantation can be safely deferred in patients with peak exercise VO_2 levels of more than 14ml/min/kg." We believe this provides adequate evidence to propose changing the qualifying requirement for VO_2 for coverage of DT to the ≤ 14 ml/kg/min that was used as the criterion for inclusion in the HeartMate II pivotal trial.

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:

- d. *have a body surface area of $< 1.5 \text{ m}^2$?*

Body surface area (BSA) is the measured or calculated surface of a human body. For many clinical purposes BSA is a better indicator of metabolic mass than body weight because it is less affected by excess body fat. Estimation of BSA is simpler than many measures of volume.

The device previously approved for destination therapy (Thoratec SNAP-VE LVAS) was a large pulsatile device weighing roughly five pounds, which was implanted in the abdomen. Because of the device size it could be difficult or impossible to implant in patients of small, short or very thin stature. For this reason, the device was limited to patients with body surface area (BSA) $> 1.5 \text{ m}^2$.

The study by Musci et al (2008) demonstrates no difference in mortality outcomes after VAD implantation for patients with low BMI compared to normal BMI. Since the correlation between BMI and BSA is about $r=0.9$, this evidence can be generalized to persons with low body surface area.

The HeartMate II is a continuous-flow device weighing approximately one pound. The small size of the HeartMate II permits implantation in a wider variety of body types. Initial data on 10 small BSA patients was analyzed by FDA for this device used for bridge to transplant, without notable adverse events

(http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040b.pdf). In order to gather data on the impact, if any, of reduced body size on patient outcomes a cohort of small body size patients, who could not be randomized in the pivotal trial, was studied and reviewed by FDA. The FDA approval no longer specifies a minimum BSA for implantation.

While implanting physicians must determine appropriate fit of the selected device for the individual patient, we propose that the evidence is adequate to remove minimum body surface area from Medicare coverage requirements.

Summary

The HeartMate II destination therapy study succeeded in meeting the pre-specified endpoints and demonstrated that overall the study subjects that received the HeartMate II device had better health outcomes than patients that received the XVE. The as-treated analysis demonstrates a substantial survival advantage for subjects treated with HeartMate II, with survival of 58% at two years. For comparison purposes the two year results for the primary endpoint of survival in the REMATCH trial was 23% for device recipients and 8 % for medical therapy patients.

The study protocol was designed to minimize study bias and the results were obtained with adequate data quality. Improvement in device durability and lower risks associated with devices such as shown in the pivotal study are critical to potentially expanding the population of device candidates to a slightly less sick patient population. Because of the relatively high use of inotropes and previously implanted devices most patients could be described by the 2009 ACC/AHA guidelines as Stage D. Risks related to VAD implantation remain significant and therefore should be carefully considered when determining device candidacy. As is the case with many of the clinical studies related to cardiac devices, patient enrollment is primarily comprised of Caucasian men. Minorities are generally underrepresented. As these devices are able to be used in smaller patients, we expect more women to be included in future studies. Studies should also enroll members of other underrepresented populations to better understand the potential for health disparities.

The overall results of the HeartMate II destination therapy pivotal study and additional literature supports changing the peak VO_2 and body size requirements. $\text{VO}_2 \leq 14$ serves as a current standard for transplant and body size requirements have and will continue to change over time as devices become smaller. Our proposal to change the medical management requirement is based on the pivotal study and that while the time on maximal medical management may be lessened by 30 days, the requirement of being treated maximally for 45 of 60 day is perhaps even more intense than the previous requirement. We are not proposing to extend coverage to Class IIIB heart failure patients. While these patients were enrolled in the pivotal study, they are a small portion of the whole group and published evidence is not available regarding their specific outcomes. However, a major consideration is the inability of heart failure specialists to replicate the entry criteria used in the pivotal study. The definition of Class IIIB was specifically for the study and is not generally accepted.

In conclusion, we propose to change the requirements for peak VO_2 , medical management and body size.

IX. Conclusion

CMS proposes the following:

The evidence is adequate to conclude that VAD implantation as destination therapy improves health outcomes and is reasonable and necessary when the device has received FDA approval for a destination therapy indication and only for patients with New York Heart Association (NYHA) Class IV end-stage ventricular heart failure, who are not candidates for heart transplant and who meet all of the following conditions:

- a. Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,
- b. Have a left ventricular ejection fraction (LVEF) < 25%; and,
- c. Have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min.

CMS is not proposing changes to any other section of 20.9 titled "Artificial Hearts and Related Devices". A comparison of the original and proposed policies can be viewed in Appendix A.

We are soliciting public comments on this proposed decision pursuant to §1862(l) of the Social Security Act.

XI. References

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Appendix A

Comparison of Proposed Changes to 20.9.B.3

3. Destination Therapy

a. VADs as Destination Therapy (effective for services performed on or after October 1, 2003, **patient selection criteria updated xx/xx/xx and** with facility criteria updated March 27, 2007)

Destination therapy is for patients that require permanent mechanical cardiac support. The VADs used for destination therapy are covered only if they have received approval from the FDA for that purpose, ~~and the device is used according to the FDA-approved labeling instructions.~~

Patient Selection

The VADs are covered for patients who have chronic end-stage heart failure (New York Heart Association Class IV end-stage left ventricular failure ~~for at least 90 days with a life expectancy of less than 2 years~~), **who** are not candidates for heart transplantation, and meet all of the following conditions:

a. ~~The patient's Class IV heart failure symptoms have failed to respond to optimal medical management, (including dietary salt restriction, diuretics, digitalis, beta-blockers, and ACE inhibitors (if tolerated) for at least 60~~**45** ~~of the last 90~~**60** ~~days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and~~

b. ~~The patient has~~ have a left ventricular ejection fraction (LVEF) < 25%;

c. **have** ~~The patient has demonstrated functional limitation with a peak oxygen consumption of ≤ 12 14 ml/kg/min; or the patient has a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion; and,~~

d. ~~The patient has the appropriate body size ($>1.5 \text{ m}^2$) to support the VAD implantation.~~

Appendix B

**20.9 - Artificial Hearts And Related Devices (Various Effective Dates Below)
(Rev. 95; Issued: 09-10-08; Effective Date: 05-01-08; Implementation Date: 12-01-08)**

A. General

A ventricular assist device (VAD) or left ventricular assist device (LVAD) is surgically attached to one or both intact ventricles and is used to assist a damaged or weakened native heart in pumping blood. Improvement in the performance of the native heart may allow the device to be removed.

An artificial heart is a biventricular replacement device which requires removal of a substantial part of the native heart, including both ventricles. Removal of this device is not compatible with life, unless the patient has a heart transplant.

B. Nationally Covered Indications

1. Postcardiotomy (effective for services performed on or after October 18, 1993)

Post-cardiotomy is the period following open-heart surgery. VADs used for support of blood circulation post-cardiotomy are covered only if they have received approval from the Food and Drug Administration (FDA) for that purpose, and the VADs are used according to the FDA-approved labeling instructions.

2. Bridge-to-Transplant

a. VADs as Bridge-to-Transplant (effective for services performed on or after January 22, 1996)

The VADs used for bridge-to-transplant are covered only if they have received approval from the FDA for that purpose, and the VADs are used according to the FDA-approved labeling instructions. All of the following criteria must be fulfilled in order for Medicare coverage to be provided for a VAD used as a bridge-to-transplant:

a. The patient is approved and listed as a candidate for heart transplantation by a Medicare-approved heart transplant center; and,

b. The implanting site, if different than the Medicare-approved transplant center, must receive written permission from the Medicare-approved heart transplant center under which the patient is listed prior to implantation of the VAD.

The Medicare-approved heart transplant center should make every reasonable effort to transplant patients on such devices as soon as medically reasonable. Ideally, the Medicare-approved heart transplant centers should determine patient-specific timetables for transplantation, and should not maintain such patients on VADs if suitable hearts become available.

b. Artificial Heart as Bridge-to-Transplant (effective for services performed on or after May 1, 2008)

An artificial heart for bridge-to-transplantation is covered when performed under coverage with evidence development (CED) when a clinical study meets all of the criteria listed below.

The clinical study must address at least one of the following questions:

- Were there unique circumstances such as expertise available in a particular facility or an unusual combination of conditions in particular patients that affected their outcomes?
- What will be the average time to device failure when the device is made available to larger numbers of patients?
- Do results adequately give a reasonable indication of the full range of outcomes (both positive and negative) that might be expected from more widespread use?

The clinical study must meet all of the following criteria:

- The study must be reviewed and approved by the FDA.
- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- The research study is well supported by available scientific and medical information, or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The research study does not unjustifiably duplicate existing studies.
- The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated it also must be in compliance with 21 CFR Parts 50 and 56.

- All aspects of the research study are conducted according to appropriate standards of scientific integrity (see <http://www.icmje.org>).
- The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for coverage with study participation (CSP) or CED coverage.
- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
- The clinical research study is registered on the ClinicalTrials.gov Web site by the principal sponsor/investigator as demonstrated by having a National Clinical Trial control number.
- The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (<http://www.icmje.org>). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

- The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability, or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The principal investigator of an artificial heart clinical study seeking Medicare payment should submit the following documentation to the Centers for Medicare & Medicaid Services (CMS) and should expect to be notified when the CMS review is complete:

- Complete study protocol (must be dated or identified with a version number);
- Protocol summary;
- Statement that the submitted protocol version has been agreed upon by the FDA;
- Statement that the above study standards are met;
- Statement that the study addresses at least one of the above questions related to artificial hearts;
- Complete contact information (phone number, email address, and mailing address); and,

- Clinicaltrials.gov registration number.

The above information should be mailed to:

Director, Coverage and Analysis Group Centers for Medicare and Medicaid Services Re: Artificial Heart Mailstop C1-09-06 7500 Security Blvd. Baltimore, MD 21244-1850

Clinical studies that are determined by CMS to meet the above requirements will be listed on the CMS Web site at: http://www.cms.gov/MedicareApprovedFacilities/06_artificialhearts.asp.

3. Destination Therapy

a. VADs as Destination Therapy (effective for services performed on or after October 1, 2003, with facility criteria updated March 27, 2007)

Destination therapy is for patients that require permanent mechanical cardiac support. The VADs used for destination therapy are covered only if they have received approval from the FDA for that purpose, and the device is used according to the FDA-approved labeling instructions.

Patient Selection

The VADs are covered for patients who have chronic end-stage heart failure (New York Heart Association Class IV end-stage left ventricular failure for at least 90 days with a life expectancy of less than 2 years), are not candidates for heart transplantation, and meet all of the following conditions:

- a. The patient's Class IV heart failure symptoms have failed to respond to optimal medical management, including dietary salt restriction, diuretics, digitalis, beta-blockers, and ACE inhibitors (if tolerated) for at least 60 of the last 90 days;
- b. The patient has a left ventricular ejection fraction (LVEF) <25%;
- c. The patient has demonstrated functional limitation with a peak oxygen consumption of <12 ml/kg/min; or the patient has a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion; and,
- d. The patient has the appropriate body size (>1.5 m²) to support the VAD implantation.

Facility Criteria

- a. Facilities must have at least one member of the VAD team with experience implanting at least 10 VADs (as bridge-to-transplant or destination therapy) or artificial hearts over the course of the previous 36 months;
- b. Facilities must be a member of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS); and,
- c. By March 27, 2009, all facilities must meet the above facility criteria and be credentialed by the Joint Commission under the Disease Specific Certification Program for Ventricular Assist Devices (standards dated February 2007).

The Web site

<http://www.cms.gov/MedicareApprovedFacilities/VAD/list.asp#TopOfPage> will be updated continuously to list all approved facilities. Facilities gaining Joint Commission certification (including prior to March 27, 2009) will be added to the Web site when certification is obtained.

Hospitals also must have in place staff and procedures that ensure that prospective VAD recipients receive all information necessary to assist them in giving appropriate informed consent for the procedure so that they and their families are fully aware of the aftercare requirements and potential limitations, as well as benefits, following VAD implantation.

b. Artificial Heart as Destination Therapy (effective for services performed on or after May 1, 2008)

An artificial heart for destination therapy is covered when performed under CED when a clinical study meets all of the criteria listed below:

The clinical study must address at least one of the following questions:

- Were there unique circumstances such as expertise available in a particular facility or an unusual combination of conditions in particular patients that affected their outcomes?
- What will be the average time to device failure when the device is made available to larger numbers of patients?
- Do results adequately give a reasonable indication of the full range of outcomes (both positive and negative) that might be expected from more wide spread use?

The clinical study must meet all of the following criteria:

- The study must be reviewed and approved by the FDA.

- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The research study does not unjustifiably duplicate existing studies.
- The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated it also must be in compliance with 21 CFR Parts 50 and 56.
- All aspects of the research study are conducted according to appropriate standards of scientific integrity (see <http://www.icmje.org>).
- The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CSP or CED coverage.

- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
- The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator as demonstrated by having a National Clinical Trial control number.
- The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (<http://www.icmje.org>). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The principal investigator of an artificial heart clinical study seeking Medicare payment should submit the following documentation to CMS and should expect to be notified when the CMS review is complete:

- Complete study protocol (must be dated or identified with a version number);
- Protocol summary;
- Statement that the submitted protocol version has been agreed upon by the FDA;
- Statement that the above study standards are met;
- Statement that the study addresses at least one of the above questions related to artificial hearts;

- Complete contact information (phone number, email address and mailing address); and,
- Clinicaltrials.gov registration number.

The above information should be mailed to:

Director, Coverage and Analysis Group Centers for Medicare and Medicaid Services

Re: Artificial Heart Mailstop C1-09-06 7500 Security Blvd. Baltimore, MD 21244-1850

Clinical studies that are determined by CMS to meet the above requirements will be listed on the CMS Web site.

http://www.cms.gov/MedicareApprovedFacilities/06_artificialhearts.asp.

C. Nationally Non-Covered Indications (effective for services performed on or after May 19, 1986)

All other indications for the use of VADs or artificial hearts not otherwise listed remain non-covered, except in the context of Category B IDE clinical trials (42 CFR 405) or as a routine cost in clinical trials defined under section 310.1 of the NCD Manual.

(This NCD last reviewed April 2008.)

Appendix C

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- * Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- * Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- * Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- * Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- * Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- * Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- * Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- * Differential assessment of outcome (detection bias).
- * Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- * Randomized controlled trials
- * Non-randomized controlled trials
- * Prospective cohort studies
- * Retrospective case control studies
- * Cross-sectional studies
- * Surveillance studies (e.g., using registries or surveys)

- * Consecutive case series
- * Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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